UNAIDS Expert Consultation

on Cognitive and Neuropsychological impairment in Early HIV infection

3–4 June 1997
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This meeting was convened and chaired

for UNAIDS by

Stuart J. Kingma, M.D.

and reported by

Lydia R. Temoshok, Ph.D.

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Contents

Participants

- James Becker, Ph.D., Neuropsychology Research Program, University of Pittsburgh Medical Center, USA

- Robert Bornstein, Ph.D., Neuropsychology Program, Ohio State University, Columbus, USA

- Prabha Chandra, Ph.D., National Institute of Mental Health & Neurosciences, Bangalore, India

- George Fein, Ph.D., Developmental Neuropsychology Laboratory, San Francisco Veterans Affairs Medical Center, USA

- Igor Grant, M.D., Department of Psychiatry, University of California, San Diego, USA

- Robert K. Heaton, Ph.D., Department of Psychiatry, University of California, San Diego, USA

- Wendy Law, Ph.D., Uniformed Services University, USA

- William Lenderking, Ph.D., Harvard Medical School/Mass General Hospital, Boston, USA

- Alex Martin, Ph.D., Laboratory of Clinical Sciences, National Institute of Mental Health, Bethesda, Maryland, USA

- Eileen Martin, Ph.D., Department of Psychiatry, University of Illinois at Chicago, USA

- Prof. Fabrizio Starace, Department of Psychiatry, University of Naples, Italy

- Yaakov Stern, Ph.D., Neurology-Sergievsky Center, Columbia University, New York, USA

Absent

- Gary G. Kay, Ph.D., Department of Neurology & Psychology, Georgetown University School of Medicine, USA

UNAIDS Staff

- Stuart Kingma, M.D., Adviser on HIV/AIDS in Institutional Settings

- Samuel Kalibala, M.D., Adviser on Care, Counselling and Social Support

- Lydia Temoshok, Ph.D., Consultant to UNAIDS

Terms of reference

Reported by
Lydia R. Temoshok, Ph.D.

The stimulus for convening this consultation was the evidence set forth in some 60 reported studies which found median rates of neurocognitive impairment in 35% of physically asymptomatic HIV-positive individuals.

Rates of impairment appear to be even higher in studies that included measurement of certain specific functions: reaction time, attention, and speeded information processing.

This suggested that it may be of critical importance to detect whether such neuropsychological changes are present in certain occupational groups. For civil and military pilots in technologically advanced countries, screening with sophisticated flight simulators and full-battery neurocognitive testing will pick up such impairment due to early HIV infection and other causes.

However, many countries do not have access to sophisticated flight simulators, and full-battery neurocognitive testing may not be available. In these situations, if the evidence of critical impairment in certain cognitive functions in early HIV infection is compelling, one recourse would be to consider the use of HIV testing as a basis for selecting (and re-certifying) candidates for piloting, related military occupational specialties and perhaps other highly technical occupations, activities, and operations.

The field of neurological and neuropsychiatric manifestations of HIV infection, including HIV neuropsychological assessment, has advanced considerably since the first reports in 1987 of early central nervous system involvement in HIV infection. Those early reports were, however, of sufficient impact to establish the basis for the US military policy of disqualifying HIV-positive pilots from flying duties. The last WHO international expert meeting on this topic was held in March, 1988.

Important developments in these areas compelled the convening of this expert consultation to delineate the state of the art and the latest findings, and to consider the implications of those findings for relevant health policy. A further rationale for such a consultation was scientific ethics. If a convincing proportion of asymptomatic HIV-positive persons have impaired performance of neurocognitive skills essential to military piloting, such that continuing to fly is considered a significant risk to the lives of others, then it is incumbent upon public health organizations to define the boundaries of such public endangerment, and to recommend policy accordingly to limit such endangerment. Public endangerment may be at stake with other military functions, analogous non-military occupations (e.g., piloting commercial aircraft, driving trains and buses, operating dangerous equipment), as well as other technical occupations which depend upon reaction time, attention, and hand-eye coordination, and where poor performance has life-or-death consequences.

A principal aim of this expert consultation, therefore, was to review evidence on the implications of neurocognitive impairment, as assessed by various instruments and methods, for real-life occupational functioning.

Glossary of key terms

Early HIV Infection (Disease)

The conclusions and recommendations in this report are focused on and limited to HIV-infected (HIV-positive) adult individuals in the early stages of HIV infection. Such individuals fit into Category A of the US Centers for Disease Control and Prevention 1993 classification scheme, and have a CD4+ cell count greater than 200. Such individuals do not have such AIDS-defining disorders as *Pneumocystis carinii* pneumonia, Kaposi's sarcoma, or tuberculosis; nor do they have significant HIV-related symptoms. Although many studies in the literature refer to HIV-positive individuals with early HIV infection as "asymptomatic", this term is not really accurate. Therefore, this report endeavours to use the term "early HIV infection" wherever possible, except when referring to literature reports of "asymptomatic" HIV-positive individuals.

Executive Functions

These encompass capacities involved in planning, initiation, solving problems, and carrying out and monitoring purposeful behavior. Such tasks are thought to be associated with the frontal lobe. Assessing executive functions involves tests that stress evaluating, planning, and then performing some type of sequential behaviour.

HIV-1-Associated Dementia (HAD) Complex

1. Marked acquired impairment in cognitive functioning (present for at least one month), involving at least two of the following ability domains: attention/concentration; speed of information processing; abstraction/reasoning; visuospatial skills; memory/learning; speech/language.
2. The cognitive dysfunction produces marked interference with daily functioning (work, home life, social activities).
3. The pattern of cognitive impairment does not meet criteria for delirium (e.g., clouding of consciousness), and there is no evidence of another pre-existing aetiology that could explain the dementia (e.g., central nervous system opportunistic infection or malignancy, psychiatric disorders, cerebrovascular disease, or severe substance abuse).

HIV-Associated Minor Cognitive/Motor Disorder (MCMD)—also referred to as HIV-Associated Mild Neurocognitive Disorder (or MND)

1. Acquired impairment in cognitive functioning, involving at least two ability domains, documented by performance of at least 1.0 standard deviation below the mean for age-education-appropriate norms on standardized neuropsychological tests, assessing at least the following abilities: verbal/language; attention/speeded processing; abstraction; memory (learned recall); complex perceptual-motor performance; motor skills.
2. The cognitive impairment produces at least mild interference in daily functioning, reduced mental acuity, inefficiency in work, homemaking, or social functioning; (a) as self-reported; (b) as observed by knowledgeable others.
3. Does not meet criteria for HIV dementia or delirium.
4. There is no evidence of another pre-existing cause for the disorder.

Magnetic resonance imaging (MRI)

MRI utilizes brain scans to produce various axial slices of the brain, which are then interpreted by a neuro-radiologist for evidence of presence and degree of cortical volume loss, central volume loss, parenchymal abnormality, and global abnormality. In addition, the scans may be analysed by quantitative morphometry to yield more precise volumetric measures of cortical fluid, subcortical/ventricular fluid, and sub-cortical white matter abnormalities.

Neurocognitive functions (processes, abilities)

Various activities by which the brain processes information, for example: perception, abstraction (conceptualization), executive functions, perceptual-motor integration, learning, and memory.

Neurocognitive impairment/disorder

A neurocognitive (neuropsychological) impairment exists when there is a deficient performance in some area of neurocognitive functioning, including attention/speed of information processing, verbal/language skills, reaction time and other perceptual/motor skills, and memory functions, including learning and recall of information. A neurocognitive disorder exists when neuropsychological impairment is accompanied by disturbances in day-to-day occupational, social, or other functioning.

Neuropsychological (NP) testing

NP testing by a qualified neuropsychologist is a useful adjunct to a neurological exam in terms of quantifying the severity of cognitive impairment and defining the patterns of disturbances. Ideally, a NP test battery should include standardized tests with published age, education, and cultural norms, which assess a range of area of cognitive functioning including verbal skills, attention/speed of information processing, abstracting abilities/executive functioning, complex perceptual motor skills, verbal and nonverbal learning, recall of verbal and nonverbal information, motor skills, and simple sensory abilities. The preferred method is to assess change in NP performance over time.

Sub-syndromic neurocognitive impairment

Acquired neurocognitive impairment that may not be as strictly documented on standardized neuropsychological tests assessing the abilities described above for MCMD, that is documented in only one ability domain, or that does not produce mild interference in daily functioning by self-report or observation by knowledgeable others.

Consensus summary and conclusions

N.B. See additional commentary in the References and Footnotes section

The diagnosis of neurocognitive impairment based on neuropsychological tests has various limitations and variability, based on the comprehensiveness of the batteries and the nature of the tests within these batteries (52); characteristics of the individuals being assessed; and settings where the tests were administered, including cultural contexts, and availability of normative standards appropriate to populations where the tests will be applied (53).

1. There is accumulating evidence of cognitive impairment in some HIV-positive individuals, even before the onset of AIDS. Studies of magnetic resonance imaging spectroscopy and morphometry, and electrophysiology show evidence of neurobiological changes in the brains of some HIV-positive individuals with early HIV disease (1-12).

2. HIV has measurable consequences for performance on neuropsychological tests of various cognitive and motor functions in some HIV-positive individuals (13-41). Impaired performance on certain tests has been linked to physiological parameters (4, 11, 12, 42-46). The majority of HIV-positive individuals in the asymptomatic stage, however, do not manifest significant neurocognitive impairment or disorder (47-49).

3. A number of studies have estimated the prevalence and degree of impairment at early HIV infection:

a) Before there is other medical evidence of AIDS, dementia has been diagnosed in less than 1% of HIV-positive individuals assessed in North American and European samples (50).

b) Minor Cognitive or Motor Disorder (MCMD) was observed in about 7% of individuals in one large (N = 600) US study (32);

c) Sub-syndromic neurocognitive impairment was ascertained in a median of 35% (range = 0 to 50%) of HIVpositive asymptomatic individuals, compared with a median of 12% (range = 0 to 42%) among appropriately matched HIV-uninfected controls, in a recent review of 57 studies (51).

4. There is a body of evidence linking performance on some neuropsychological measures to occupational competence (54-58). Not all cognitive deficits, however, as measured by neuropsychological tests, have implications for real-life performance.

5. There are only a few studies regarding the relationship of HIV neurocognitive impairment to real-life performance in specific occupations or job classifications among pre-AIDS individuals (e.g., 54, 58). More research in this area is urgently needed.

6. Various factors, besides HIV infection, have been shown to affect the appearance and/or the measurement of neurocognitive deficits, including: alcohol and drug use (59-62; prescription medicine use; prior or concurrent psychiatric, neurological, or medical conditions; demographic factors such as age, education, and ethnicity; nutritional status; and developmental history (31, 37, 63-67).

7. Where neurocognitive impairment in performance has implications for public safety (that is, occupations or situations in which large numbers of persons could be affected by impaired performance or error by one individual, such as a pilot, train engineer, bus driver, or the like), it is recommended that HIV-positive individuals undergo neurocognitive evaluation on a periodic basis, such as every 6 months (68).

8. It is not recommended that HIV-positive individuals be excluded from any occupation on the basis of HIV infection alone (69).

9. Periodic neurocognitive evaluation should assess those skills and abilities necessary, appropriate, and relevant for an individual's specific occupation or performance requirements, and would ideally be based on computerized simulators which are as close as possible to mimicking or depicting real-life performance conditions (54, 70, 71). In the absence of such simulators, it is recommended that neurocognitive evaluation be based on a comprehensive battery of neuropsychological tests (72), which, at minimum, should assess the following domains:

- speed of information processing, including simple and complex (choice) reaction time;
- learning efficiency;
- attention, both selective and divided;
- executive functions, including planning and flexibility;
- working memory;
- delayed retention; and
- motor and perceptual-motor speed.

10. The effects of the new protease inhibitors and antiretroviral combination therapies on neurocognitive functioning have not been assessed, although there have been some studies of neurocognitive effects of zidovudine (AZT; 73-76). It is strongly recommended that all clinical trials of these treatments include objective assessment of consequences for neurocognitive functioning (based on a comprehensive battery of tests assessing the domains listed in #9 above), including possible positive and negative effects of the treatments (77).

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and footnotes

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ref. 51: footnote

This systematic review of 30 studies which compared rates of neuropsychological impairment in asymptomatic HIV+s and controls calculated a median rate of 12% impaired among HIV- controls (range 0-42%) and 35% for asymptomatic HIV+s (range 0-50%).

ref. 52: footnote

Some commentators in the field have assumed that the results of larger-size neuropsychological studies are necessarily more reliable and valid because of their heightened power (Newman SP, Lunn S, Harrison MJG. Do asymptomatic HIV-seropositive individuals show cognitive deficit? AIDS *1995; 9:1211-1220.). However, because of the costs and time involved in administering a comprehensive battery, most large-scale studies, such as the MACS (47), have employed smaller, non-comprehensive batteries, which, as discussed above, tend not to reveal neurocognitive impairment in early HIV infection. One of the notable exceptions to this observation is the "HNRC 500", which combines a large-size sample with a comprehensive battery (32). Therefore, the size, per se, of neuropsychological studies should not be used as the sole criterion to evaluate their methodology adequacy; in fact, unless a comprehensive battery was used, a large-scale study may lead to false confidence as well as to possibly erroneous conclusions about the extent and frequency of neurocognitive impairment in early HIV disease.*

There appears to be good evidence that neurocognitive changes in early HIV infection reflect more of a subcortical pattern of neurocognitive impairment (43, 49), while later manifestations of HIV-associated brain disease tend to involve impairments in more cortical areas. These considerations might be another explanation for the seemingly discrepant findings in the literature: studies that only included tests of "higher" cognitive functioning (e.g., abstraction, naming) would tend to find fewer differences between HIV+ individuals and controls, while those studies that included a broader range of tests, especially tests of reaction time, attention, and speeded information processing, which are most commonly impaired in HIV+ individuals (followed by difficulties in verbal fluency and motor speed), would find more differences.

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52. It seems clear that finding evidence of impairment in early HIV infection depends on the size of the test battery used, as White *et al*. (51) demonstrated in their review of 30 studies. Among studies that used small batteries, most reported findings failed to find differences between "asymptomatic" HIV-positive individuals and controls. Studies with medium-sized batteries were sometimes suggestive but inconclusive. The majority of studies using more comprehensive test batteries found significant impairment in asymptomatic individuals. Compared to studies that used brief or intermediate screening batteries, those with comprehensive testing were about three times more likely to find an increased rate of neurocognitive impairment in asymptomatic HIV-positive individuals (51).

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ref. 62: footnote

Preliminary data from the Italian Neuropsychological HIV Study suggest that «cerebral reserve» could be reduced in intravenous drug users (IVDUs), as a consequence of chronic exposure to the substance of abuse, so that these individuals become more vulnerable to direct and indirect neurotoxic effects of HIV (Starace F, Baldassarre C, Biancolilli V, Fea M, Serpelloni G, Bartoli L, & Maj M. Early neuropsychological impairment in HIV-seropositive IVDUs. Unpublished data, abstract presented at the UNAIDS Expert Consultation, Washington DC, 5 June 1997).
Further research is necessary on alcohol use, drug use, and other factors which may also interact with HIV in deleterious ways.

62. Findings of some recent studies (59-61) suggest that alcohol consumed in even moderate quantities by HIV-positive individuals may have lasting effects on cognitive performance. Therefore, it is recommended that HIV-positive individuals involved in occupations with implications for public safety do not consume alcoholic beverages at any time.

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ref. 68: footnote

[Additional footnote by UNAIDS: In this context of occupational performance which has implications for public safety, UNAIDS believes that cognitive and neuropsychological evaluation on a periodic basis would be important for all persons who may have neurocognitive deficits from any cause, not just those that may be related to HIV.]

68. It should be noted that the course of HIV-related cognitive impairment over time is not necessarily linear or progressive. Some recent data suggest that a certain percentage of individuals who have evidence of subsyndromic impairment or of MCMD at one point in time test within normal limits one year later (50). Therefore, it is recommended that HIV-positive individuals who may be excluded from certain tasks or occupations on the basis of neurocognitive testing at one point in time should be periodically retested to determine if their performance has improved to within normal limits for a given occupation or function.

69. Although UNAIDS does not recommend HIV testing as a replacement for valid neurocognitive evaluation, some public health experts have suggested that HIV testing could be used as a complementary strategy in the following ways:

a) In some countries with high HIV prevalence and limited resources to conduct extensive neuropsychological testing, periodic HIV screening of individuals engaged in occupations with implications for public safety is being used for identifying HIV-positive individuals who could then be followed medically and neuropsychologically every six months. This can represent a significant savings for countries with limited resources for occupational or neuropsychological testing, because it reduces the number of persons requiring this extensive periodic testing.

(b) As long as an HIV+ person performs within the same acceptable range as do uninfected individuals in the same occupation on work simulation tasks (a more ideal assessment), or appropriate neuropsychological tests, then the individual should be allowed to continue to work in this occupation (cf. 68).

(c) Early identification of HIV infection may be helpful in counseling individuals to avoid certain situations or activities, such as alcohol use, which recent studies have indicated can significantly and negatively impact job performance in HIV-positive persons, even when consumed in modest quantities (cf. 62).

(d) Early identification of HIV infection would also be helpful to the individual by allowing treatment to be initiated early. This may help slow down disease progression, and may well significantly reduce neuropsychological impairment, allowing the individual to remain productively engaged in work.

70. Mapou RL, Law WA, Kay GG, Clasby S, Roller T, Temoshok LR. Performance on conventional and computerized reaction-time measures in HIV-1 infected individuals. *J Int Neuropsychol Soc* 1995; 1:162-3.

ref. 71: footnote

Another neurocognitive assessment battery, designed to produce a standardized method that is responsive to military-mission abilities and skills, and to detect performance decrements due to the use of biomedical treatment drugs, is currently in use (Eglund CE, Reeves DL, Shingledecker CA, Thorne DR, Wilson KP, Hegge FW. Unified Tri-Service Cognitive Performance Assessment Battery (UTC-PAB): Design and specification of the battery. Report No 87-10. Naval Health Research Center, P.O. Box 85122, San Diego, CA 92139.). This battery has not, however, been evaluated or validated for neurocognitive screening in HIV+ military personnel.

71. Civilian researchers working with military populations recommended development of computerized neurocognitive measures to assess skills presumed important for aviation as an alternative to mandatory exclusion of HIV-positive pilots from flying in the US military (54). One such technology is CogScreen, an 11-test, 45-minute computer-administered and scored neurocognitive battery, designed to assess deficits or changes in attention, immediate and short-term memory, spatial-perceptual functions, calculation skills, reaction time, simultaneous information processing, and executive functions. The Cog Screen-Aeromedical Edition (CogScreen-AE, currently available at a cost of about $900) was designed to detect subtle changes in cognitive functioning, which left unnoticed, may result in poor pilot judgement or slow reaction time in critical operational situations. (Kay, GG. CogScreen Aeromedical Edition: Professional Manual. Odessa, FL.: Psychological Assessment, 1995). More than 900 commercial pilots have participated in CogScreen studies, which have demonstrated expected relationships with analogous non-computerized neuropsychological tests, and differential aviation performance. A recent study focused on applications of CogScreen-AE in the evaluation of head-injured military aviation personnel (Moore JL, Kay GG. CogScreen-Aeromedical edition in the assessment of the head injured military aviator. Conference Proceedings, Aerospace Medical Panel Symposium, Advisory Group for Aerospace Research and Development. Koln, Germany, 9-12 October, 1995). Because CogScreen included response speed and other neurocognitive domains found to be affected in HIV disease, it was believed that it could provide a foundation for investigating performance of HIV-positive military aviators. There is, however, only preliminary data comparing CogScreen and standard neuropsychological tests, including RT, in HIV-positive military samples.

72. Butters N, Grant I, Haxby J, Judd LL, Martin A, McClelland J, Pequegnat W, Schacter D, Stover E. Assessment of AIDS-related cognitive changes: Recommendations of the NIMH workshop on neuropsychological assessment approaches. *J Clin Exp Neuropsychol* 1990; 12:963-978.

73. Schmitt FA, Bigley JW, McKinnis R, et al. Neuropsychological outcome of zidovudine (AZT) treatment of patients with AIDS and AIDS-related complex. *N Engl J Med* 1988; 319:1573-1578.

74. Sidtis JJ, Gatsonis C, Price RW, et al. Zidovudine treatment of the AIDS dementia complex: Results of a placebo-controlled trial. *Ann Neurol* 1993; 33:343-349.

75. Martin EM, Pitrak DL, Pursell KJ, Andersen BR, Mullane KM, Novak RM. Reaction times and antiretroviral therapy in HIV-1 infection. *J Intl Neuropsychol Soc*, in press.

76. Martin EM, Pitrak DL, Novak RM, Pursell KJ, Mullane KM. Reaction times are faster in HIV-seropositive patients on antiretroviral therapy: A preliminary report. *J Neuro-AIDS*, in press.

77. It cannot be assumed that reduction of HIV load to "undetectable" levels in peripheral blood means that HIV is not present in the cerebrospinal fluid or in the brain. It is theoretically possible for a HIV-positive individual to appear physically healthy and "free" of HIV, but still to have evidence of HIV-related neurocognitive impairment. This is another reason for including objective assessment of neurocognitive functioning in a all clinical trials of protease inhibitors and antiretroviral combination therapies. Until such research is done, and in the absence of case-by-case, periodic neurocognitive testing, it is not recommended that HIV-positive individuals who are receiving such treatments be automatically reinstated in occupations involving public safety, assuming they had previously been excluded from such work on the basis of HIV and/or neurocognitive testing.